REMARKS

Claims 1-16 were previously cancelled. Claims 19-22, 24-48, and 52-54 are cancelled herein without prejudice to revival for prosecution in a continuation or divisional application. New claims 56-59 have been added. Accordingly, claims 17, 18, 23, 49-51, and 55-59 are currently pending.

The amendments to the claims add no new matter.

New claims 56, 57, 58, and 59 are related to previous claims 21, 22, 31 and 32, respectively.

Claims 17 and 51 have been amended to recite that the polypeptide transduces an increase in intracellular calcium. Support for the amendment can be found, *e.g.,* on page 14, paragraph 65; and page 16, paragraph 70 at line 19.

Claims 18 and 51 recite a nucleic acid encoding a polypeptide comprising at least 200 contiguous amino acids of SEQ ID NO:18. Support can be found, *e.g.,* in the specification at page 22, paragraph 93.

Claim 23 recites stringent hybridization conditions comprising 50% formamide, 5X SSC and 1% SDS at t 42°C and wash conditions comprising 0.2XSSC and 0.1% SDS at 65°C. Support can be found, *e.g.,* in the specification on page 25 in paragraph 98.

For convenience, the objections/rejections will be addressed in the order presented in the Office Action mailed October 10, 2003.

Information Disclosure

Enclosed herewith is an English abstract of JP 2001-245666. Applicants also note that the sequences disclosed in the Japanese application employ English letters.

Claim objections

Claims 17-25 and 49-55 were objected to for reciting a non-elected invention. The claims have been amended to delete the non-elected sequences, SEQ ID NOs:15 and 16.

Objections to the specification

The amendments to the specification address the objections presented by the Examiner. Paragraph 66 has been amended to delete "therefore" at the indicated sentence and to correct placement of quotation marks. Paragraph 7 has been amended to delete the hyperlink.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 17, 20, 25, 51, and dependent claims 18, 19, 21-23, 31, 32, 49, 50, and 52-55 were rejected as alleged indefinite.

Claims 17 and 20 were rejected as indefinite in the use of the term "G-protein coupled receptor polypeptide" in claim 17 in conjunction with the "G-protein coupled receptor activity" term in claim 20. Applicants believe that this rejection is obviated by the cancellation of claim 20. In addition, claim 17 has been amended to recite that the polypeptide transduces an increase in intracellular calcium.

Claims 20 and 51 were rejected as allegedly indefinite in the recitation of "G-protein coupled receptor activity." The rejection is moot as applied to claim 20 in view of its cancellation. Claim 51 has been amended to recite that the polypeptide transduces an increase in intracellular calcium. Applicants therefore request withdrawal of the rejection.

The rejection of claim 25 as indefinite in the recitation of "moderately stringent hybridization conditions" is rendered moot by the cancellation of the claim.

Rejections under 35 U.S.C. § 101/112, first paragraph

Claims 17-25, 31, 32, and 49-55 were rejected as allegedly lacking utility. The Examiner argues that mouse TGR346b is an orphan GPCR with no ligand or substantial activity identified, and that the utilities disclosed in the application are generally applicable to any receptor and therefore are not specific or substantial. Further, the Examiner contends that no specific function has been assigned to human TGR346 and thus mouse TGR346 would not have utility based solely on its homology to the human sequence. Applicants respectfully traverse. The claimed nucleic acid compositions are fully compliant with the utility requirements under 35

U.S.C. § 101 because identification of the TGR346 nucleic acids permits one of skill in the art to, for example, screen for agonists or antagonists of TGR346 activity, which can be used, *e.g.*, for modulating TGR346 activity in brain cells.

mTGR346b has GPCR activity

GPCR polypeptides encoded by the claimed nucleic acid sequences have GPCR activity. Enclosed herewith is a declaration by Hui Tian, Ph.D. that provides additional evidence supporting the utility of Applicants' invention. The Declaration presents data showing that murine TGR346b, which is encoded by SEQ ID NO:17, has a known G-protein coupled receptor activity, *i.e.*, it transduces an increase in intracellular calcium. Dr. Tian explains that GPCR activity can be assessed using a variety of common assays. One such assay is an Aequorin assay. Aequorin assays are widely used in the art to measure GPCR-mediated increases in intracellular calcium. The assay involves the use of the Ca^{2+}-sensitive photoprotein aequorin. The aequorin complex contains the apo-aequorin protein, molecular oxygen, and the luminophore coelenterazine. The binding of calcium ions disrupts the complex, leading to the emission of blue light, which provides a means of determining increases in intracellular calcium.

As presented in the Declaration, mouse TGR346b GPCR activity was tested in an Aequorin assay. The results demonstrate that mouse TGR346b transduces an increase in intracellular calcium.

The specification teaches that GPCR activity can be assessed using a variety of assays to determine functional effects. These include changes in calcium ion levels (see, *e.g.*, page 16, lines 4-9, paragraph 9). The exemplary data provided in the Declaration provide additional evidence that mouse TGR346b has a GPCR activity, as is asserted in the specification.

mTGR346b has specific and substantial utility

Further, the application teaches that mouse TGR346b is expressed in the brain (*e.g.*, page 72, paragraph 268) and that the protein can be used to identify specific modulators of GPCR activity, *i.e.*, TGR346b activity, in this type particular cell type or tissue (*see, e.g.*, page 6, paragraphs 20-22; and in paragraph 45, at lines 2-8 of page 10). For example, the mouse nucleic

acid sequence may be useful in generating transgenic animals that can be used for screening for modulators *in vivo* (*see, e.g.,* page 55, paragraph 205). Dr. Tian's Declaration provides additional evidence that one of skill in the art recognizes that the sequences have utility, *e.g.,* they can be used to identify modulators of GPCRs for regulating TGR346 activity in cells such as brain cells. These statements are additionally supported by the utilities set forth in WO200116316 (Ref AX in the IDS submitted March 25, 2003), WO200204518 (Ref AKK), and WO200078809 (ref AT).

The disclosure of the mouse TGR346b coding sequences for GPCRs expressed in brain and its functional characterization, combined with the methods disclosed in the specification and the level of skill in the art, is sufficient to establish a credible, specific, and substantial utility in accordance with the definitions provided in the MPEP (§§ 2107.01 and 2107.02). The utility is specific--it relates to TGR346 activity, not an unspecified biological activity (MPEP § 2107.01(I)). It is substantial--it relates to a "real world" use. As noted above, compounds that regulate TGR346 can be identified as described in the specification. The invention therefore has a real-world use for identifying modulators of brain cell physiology (MPEP § 2107.01(I)).

The utility is also credible. "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicants' assertion." (MPEP § 2107 (II)). The rejection provides no evidence or reasoning as to which one of skill in the art would not find the utility to be credible.

a product based on an invention need not be available to satisfy the utility requirement

Our patent law encourages early disclosure of inventions. The MPEP at § 2107.01(I)), referring to *Brenner v. Manson,* 148 USPQ 689, 695 (US Sup. Ct. 1966) reminds Office personnel "to be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement."

In *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980), the CCPA was additionally instructive on this point.

The Court was confronted with an issue in which the claimed compound, 16-phenoxy-substituted prostaglandin (PG), was shown to have some pharmacological activity, *i.e.*, causing changes in blood pressure in the rat blood pressure (BP) test and stimulation of smooth muscles in the gerbil colon smooth muscle stimulation (GC-SMS) test, yet no specific therapeutic use for the compound was established. In deciding the question of utility, the CCPA stated:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illness and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many as compounds as possible, we conclude that adequate proof of any such activity constitute a showing of practical utility.

Nelson, 206 USPQ at 883. The present case is analogous to *Nelson*. TGR346 has GPCR activity and is expressed in the brain. Compounds capable of modulating TGR346 activity can be identified using mouse TGR346b. In keeping with the reasoning advanced in *Nelson,* assays for screening of TGR346 modulators is beneficial to the public and the disclosure of how to perform these assays should be encouraged. The present application provides just this kind of disclosure. To hold that the present invention lacks sufficient utility under 35 U.S.C. §101 to warrant patent protection would be inconsistent with the underlying policy of case law and create a strong disincentive for researchers to disclose their inventions of this type.

In view of the foregoing, Applicants respectfully request withdrawal of the utility rejection and associated rejection under 35 U.S.C. § 112, first paragraph.

Priority

The Examiner states that the provisional applications which were cited in the claims for priority do not disclose the sequences of SEQ ID NO:17 or SEQ ID:18 and that the effective filing date of the application is therefore November 21, 2001. Although Applicants do

not necessarily agree with the Examiner's conclusion, we believe that there is no intervening art, and that the priority dates therefore does not matter with regard to patentability of the claimed subject matter. The Examiner also states that even if the claimed sequences were disclosed, the provisional applications fail to provide adequate support under 35 U.S.C. § 112, first paragraph. Without acquiescing to the Examiner's positions, Applicants assert that the priority date to which they are entitled is not germane to patentability.

Rejection under 35 U.S.C. § 102

Claims 17, 19, 23-25, 31, 32, 49, and 50 were rejected as allegedly anticipated by WO200022131. The Examiner argues that this reference teaches a GPCR (referred to as hRUP4) that has greater than 95% identity to SEQ ID NO:18 because identity determination as described in the specification is not limited to the length of the complete sequence. The Examiner further contends that because there are extensive regions of identity between hRUP4 and SEQ ID NO:18, one of skill would have reasonably expected that the encoded hRUP4 would be specifically bound by a polyclonal antibody generated against SEQ ID NO:18; that a nucleic acid encoding SEQ ID NO:18 would have reasonably expected to specifically hybridize under stringent conditions to a nucleic acid encoding hRUP4; and that a nucleic acid encoding hRUP4 would be amplified by primers that specifically hybridize to SEQ ID NO:17. The rejection is partially obviated due to the cancellation of claims 19, 24, 25, 31, and 32. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

Claim 17 has been amended to recite a nucleic acid encoding a polypeptide comprising greater than 85% amino acid identity to the amino acid sequence of SEQ ID NO:18. The claim explicitly refers to percent identity in context of the full-length sequence, *i.e.,* the amino acid sequence of SEQ ID NO:18, not a subsequence of SEQ ID NO:18. The sequence comparison provided by the Examiner shows 81.4% identity between SEQ ID NO:18 and hRUP4. Thus, the cited sequence does not provide all of the elements set forth in claim 17 and therefore does not anticipate claim 17.

Similarly, with regard to the Examiner's arguments that a nucleic acid encoding mTGR346b, or a region thereof, would hybridize under stringent condition, the amended claims

recite characteristics of the claimed sequences that are not disclosed in WO200022131. Thus, this aspect of the rejection has also been obviated.

Claims 17, 20, 25, 31, 32, 49, and 50 were also rejected as allegedly anticipated by Rose *et al.* The rejection alleges that Rose *et al.* teach a GPCR that has greater than 95% identity to SEQ ID NO:18 because percent identity could be determined over any region of SEQ ID NO:18. As explained above, the percent identity set forth in the claims is determined over the full length of SEQ ID NO:18. Accordingly, Rose *et al.* do not anticipate Applicants' invention.

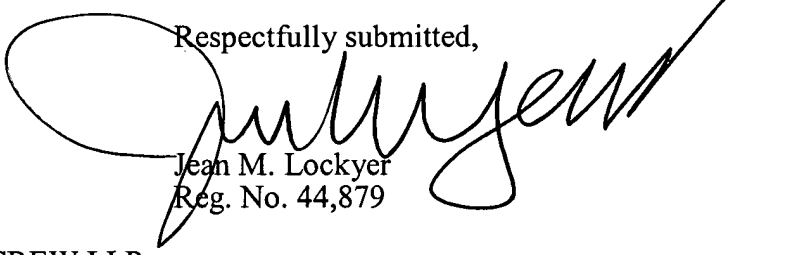
In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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